## REMARKS/ARGUMENTS

Claims 39-44 are pending in this application and are rejected on various grounds. Claim 44 has been canceled without prejudice or disclaimer. The rejections to the remaining claims are respectfully traversed.

### Priority

The Examiner states that Applicants are entitled to the priority of PCT application PCT/US00/04414 filed February 22, 2000, based on inhibition of adrenal cortical capillary endothelial cells. However, Applicants rely on the data generated in the MLR assay (Example 74), first disclosed in U. S. Application Serial No. 60/100,858 filed September 17, 1998, which establishes patentable utility for the claimed invention.

Applicants submit that the PRO217 polypeptide, to which the presently claimed antibodies are raised, stimulates T cell proliferation in the MLR assay and this is described in Example 74, page 208 of the specification. MLR is a well-established assay for evaluating test compounds, like polypeptide PRO217 for their ability to stimulate T lymphocyte proliferation *in vitro*, and consequently, for assessing the immune response of an individual. The MLR assay is well-described in standard textbooks, including, for example, *Current Protocols in Immunology*, unit 3.12; edited by J E Coligan, A M Kruisbeek, D H Marglies, E M Shevach, W Strober, National Institutes of Health, Published by John Wiley & Sons, Inc., which is referenced in Example 74, and, the entire content of which is expressly incorporated by reference into the disclosure of the present application. In brief, in this method, an immune response results upon mixing T cells from antigenically distinct individuals under cell culture conditions. An MLR reaction can be monitored qualitatively, for example, by following the incorporation of tritiated thymidine during DNA synthesis, or, by observing blast formation, or by other methods well known in the art.

Applicants further submit that the MLR assay has been extensively used and is the best *in vitro* model for screening immunosuppressive agents for use in the prevention of graft-versus-host disease and graft rejection. It is well known that the transplantation of tissues or organs between individuals with MHC incompatibilities

quickly activates the recipient's immune system which then attempts to destroy the transplanted tissue or organ. Transplantation across minor histocompatibility loci generally induces a more indolent response. Physicians analyze the major and minor histocompatibility differences to predict the success of the graft and to adjust the aggressiveness of immunosuppressive therapy.

Inhibitors of MLR find utility in suppressing unwanted immune response, and thus suppresses unwanted graft rejection. For example, the ability of tepoxalin, an immunomodulatory compound, to suppress graft-versus-host reaction, has been demonstrated using the MLR assay (Fung-Leung *et al.*, *Transplantation* 60:362-8 (1995)). Other immunosupressants have also been routinely identified using the MLR assay. For example, the immunosuppressive efficacy of SNF4435 and D, produced by a strain of Streptomyces spectabilis, has been tested using the MLR assay. As recently as 2002, the immunosuppressive effect of tautomycetin (TMC) was assessed with mixed lymphocyte reactions, and confirmed *in vivo* using TMC-treated rats that received a heterotopic cardiac allograft (Shim *et al., Proc. Natl. Acad. Sci USA* 99(16):10617-10622 (2002)). The authors were confident to conclude from the MLR data : "TMC has the capacity to inhibit the intracellular signaling pathway leading to T cell activation and proliferation . . . " (page 10621, second column).

In conclusion, the art as a whole clearly establishes that the mixed lymphocyte reaction (MLR) is a widely used *in vitro* assay for identifying immunosuppressant compounds.

Regarding "real-life" diseases where the stimulation of lymphocyte proliferation would be beneficial, Applicants submit that in 1998, it was well known in the art, as it is today, that T-cells are highly instrumental in the body's natural defense mechanism fighting infections. For example, viral infections, such as HIV infection, are well known to result in reduced T cell count. Indeed, the count of T-cell lymphocytes is a generally accepted measure of the extent and seriousness of HIV infection and resultant AIDS. Accordingly, stimulators of T-cell proliferation find utility in fighting viral infections, including retroviral infections, such as HIV infection or Epstein-Barr infection. Consequently, antagonistic antibodies to peptide PRO217 can also be used to suppress

the T cell stimulatory activity of peptide PRO217 in conditions such as graft rejection or graft vs. host disease.

Accordingly, Applicants have asserted a substantial, specific and credible utility for the presently claimed antibodies and submit that, as a result, all claims are entitled to an effective filing date of September 17, 1998.

## Specification

Applicants have amended the specification to remove the hyperlinks embedded in the specification, as indicated by the Examiner.

## Double Patenting

Claim 44 was objected to under 37 C.F.R. §1.75 as being a substantial duplicate of Claim 39. Since Claim 44 has been canceled, this double patenting rejection should be withdrawn.

## Claim Rejections – 35 U.S.C. §101

Claims 39 and 44 were rejected under 35 U.S.C. §101 allegedly because the claimed invention was directed to non-statutory subject matter.

Applicants have canceled Claim 44 without prejudice and have amended Claim 39 to recite an "isolated" antibody. This should overcome this rejection and Applicants request that this rejection be withdrawn.

## Claim Rejections – 35 U.S.C. §112

Claims 42 and 44 were rejected under 35 U.S.C. §112, second paragraph, allegedly for being indefinite because the Examiner asserted that "an antibody could not be both an antibody and an antibody fragment. Applicants respectfully traverse this rejection.

Claim 44 has been canceled. This rejection is traversed as applied to amended Claims 39 and 42.

Applicants submit that the definition of "antibody" includes "antibody fragments" and have been well-defined on page 75, line 38 onwards. As the Examiner is aware,

Applicants can be their own lexicographer and hence Claims 39 and 42 are definite and this rejection should be withdrawn.

Claim 44 was rejected for being indefinite in reciting "specifically" which allegedly was not defined in the specification and whose metes and bounds were not clear.

Applicants submit that the art-recognized meaning of "specific" binding is that the antibody specifically binds to an antigen and does not significantly cross-react with another antigen. However, solely to simply issues and to facilitate prosecution of this case, Claim 44 has been canceled and Claim 39 has been amended to recite specific binding. Accordingly, the present rejection should be withdrawn.

**Claim Rejections - 35 U.S.C. §102**

11) Claims 39 and 44 were rejected under 35 U.S.C. §102 (a) as allegedly being anticipated by Hsieh *et al.* (Nature 398: 431-36, 1999) which discloses a polypeptide with 99.7% sequence identity to SEQ ID NO: 4 of the present application.

In view of the discussions under priority, the "stimulation of proliferation of T-lymphocytes assay" provides patentable utility and has a priority date of September 17, 1998. The effective reference date of Hsieh is 1999 which is after the effective filing date of the present application. Thus, Applicants submit that Hsieh is not a proper prior art reference under § 102(a).

Hence, Applicants respectfully request withdrawal of this rejection.

12) Claims 39-44 were rejected under 35 U.S.C. §102 (b) as allegedly being anticipated by Brewer *et al.* (WO 98/54963; published December 10, 1998) which discloses a polypeptide approximately 99% identical to polypeptide of SEQ ID NO: 4 of the present application.

Again, in view of the discussions under priority, the effective filing date of the present application is September 17, 1998. The effective reference date of Brewer is December 10, 1998 which is after the effective filing date of the present application.

Thus, Applicants submit that Brewer is not proper prior art under 35 U.S.C. §102(b) or §102(a) and respectfully request withdrawal of this rejection.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-1618 P2C8**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: December 10, 2003

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